Trans. Ky. Acad. Sci., 39(1–2), 1978, 23–30

Conjugate Addition Reactions of 4-Chlorobenzotriazole, 4,6-Dichlorobenzotriazole, and 4,5,6,7-Tetramethylbenzotriazole

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ABSTRACT

4-Chlorobenzotriazole, 4,6-dichlorobenzotriazole, and previously undescribed 4,5,6,7-tetramethylbenzotriazole were synthesized and subjected to some base-catalyzed conjugate addition reactions. Addition products of 4-chloro- and 4,6-dichlorobenzotriazole with acrylonitrile, acrylamide, crotonic acid and benzalacetophenone were prepared, as well as an addition product of 4,5,6,7-tetramethylbenzotriazole with crotonic acid. Structural assignments were made on the addition products from ultraviolet absorption data; 4-chlorobenzotriazole giving 1- and 2-substituted products, and 4,6-dichloro- and 4,5,6,7-tetramethylbenzotriazole giving only 2-substituted products. Postulations are advanced on the basis of inductive and steric effects in an effort to explain the influence of benzenoid substituents on the course of the addition reaction.

INTRODUCTION

It has been reported previously that azoles with an unsubstituted, exocyclic imino group undergo addition reactions with conjugated, unsaturated systems (Wiley et al. 1954, 1955). Several benzenoid substituted benzotriazoles were later synthesized and addition products prepared and structurally elucidated by ultraviolet absorption data (Wiley, Hussung, and Moffat 1955; Wiley and Hussung 1957). The reported evidence indicated that benzotriazoles with chlorine atoms substituted in both the 4- and 7-positions (4,5,6,7-tetrachlorobenzotriazole and 4,7-dichlorobenzotriazole) add to conjugated systems to give 2-substituted products, whereas 5,6-dichlorobenzotriazole along with the parent, benzotriazole, yielded 1-substituted products. This difference in behavior was attributed to steric hindrance when bulky substituents occupy both the 4- and 7-positions.

In order to obtain a clearer understanding of the effect of benzenoid substituents of benzotriazoles on the course of the addition reaction, 4-chlorobenzotriazole, 4,6-dichlorobenzotriazole, and 4,5,6,7-tetramethylbenzotriazole were prepared and subjected to the base-catalyzed azole addition reaction and the structure of the products elucidated.

ACKNOWLEDGMENT

Partial support of this research by the Murray State University Committee on Institutional Studies and Research is gratefully acknowledged.

MATERIALS, METHODS, AND RESULTS

The synthesis of 4-chlorobenzotriazole was accomplished by 3 different methods. The first involved the direct chlorination of benzotriazole utilizing the swamping catalyst technique, in which excess aluminum chloride is used as a complexing agent (Gordon and Pearson 1964). An equimolar amount of chlorine was passed into the molten mass of benzotriazole and aluminum chloride to produce 4- and 5-chlorobenzotriazole and some dichlorinated products. A mixture of the monochloro derivatives was separated from the much less soluble dichloro derivatives by fractional recrystallization from water. The mixture melted over a wide range (136–155 C) and gave a neutralization equivalent identical with that of the calculated value (153.5). An attempt to separate the mixture using ethanol and aluminum oxide in a column chromatographic technique failed. Separation of the isomers was accomplished, however, by fractional recrystallization from a 1:2

ethanol–water mixture. The less soluble 4-chlorobenzotriazole was isolated in 9 percent yield.

The second method employed to prepare 4-chlorobenzotriazole involved replacement of the amino group in 4-aminobenzotriazole via the Sandmeyer reaction. Readily available 4-nitrobenzotriazole (Fries et al. 1934) was reduced catalytically and the resulting amino derivative diazotized. Replacement of the diazonium group was effected by addition of a freshly prepared cuprous chloride solution. After completion of the reaction, 4-chlorobenzotriazole was obtained in 4 percent yield.

The third and most satisfactory method of preparation of 4-chlorobenzotriazole was by ring closure that involved diazotization of 3-chloro-o-phenylenediamine formed during catalytic hydrogenation of 6-chloro-2-nitroaniline. The precursor of the diamine was obtained as follows. Sulfonation of o-nitroaniline gave 3-nitro-4-aminobenzenesulfonic acid that was chlorinated, using chlorine gas dissolved in glacial acetic acid, to give 3-nitro-4-amino-5-chlorobenzenesulfonic acid (Wolf et al. 1954) that in turn was desulfonated during steam distillation to give 6-chloro-2-nitroaniline.

4,6-Dichlorobenzotriazole was synthesized as previously described (Wiley and Moffat 1963) by diazotization of 3,5-dichloro-1,2-diaminobenzene, obtained by the stannous chloride and hydrochloric acid reduction of 2-nitro-4,6-dichloroaniline.

Previously undescribed 4,5,6,7-tetramethylbenzotriazole was prepared as follows. Pentamethylbenzene was nitrated below 10 C with a mixture of fuming nitric acid and concentrated sulfuric acid covered with an equal volume of chloroform to give very good yields of dinitroprehnitine (Smith and Harris 1935). The dinitroprehnitine was suspended in glacial acetic acid, palladium on charcoal was added and reduction was effected using a Parr hydrogenator. The resultant tetramethyl-o-phenylenediamine was diazotized in the acetic acid medium with nitrous acid to yield 4,5,6,7-tetramethylbenzotriazole.

The addition products were prepared, in general, by heating the substituted benzotriazole with the conjugated substrate for 15–20 hours in the presence of a base catalyst, either pyridine or benzyltrimethylammonium hydroxide.

Some experimental details for the preparation and characterization of the parent benzotriazoles and their conjugate addition products follow.

4-Chlorobenzotriazole

To 22.9 g (0.133 mole) of 6-chloro-2-nitroaniline dissolved in 300 ml of glacial acetic acid was added 0.5 g of palladium on charcoal catalyst. The mixture was placed on a Parr hydrogenator overnight to reduce the nitroamine to 3-chloro-o-phenylenediamine. The resultant solution was filtered, cooled to 5 C, and an aqueous solution of sodium nitrite was added dropwise with stirring until an excess of nitrous acid was observed. The solution, after being allowed to warm slowly to room temperature, was concentrated to approximately 30 ml and diluted with water to precipitate 12.2 g of the crude product that was 60 percent of the theoretical amount. Decolorization with norite and several recrystallizations from water gave the pure product, mp 169–171 C. The reported melting point is 170 C (Dal Monte and Veggetti 1958).

β-1′-(4′-Chlorobenzotriazolyl)-butyric acid

To a melt of 1.53 g (0.01 mole) of 4-chlorobenzotriazole and 1.30 g (0.014 mole) of crotonic acid (10% water) was added 20 drops of pyridine. The mixture was heated at 100 C for 15 hours, cooled, dissolved in a few milliliters of acetone and poured into 0.5N hydrochloric acid. The resultant solution was decolorized with norite and, upon cooling, a tan oil separated that eventually solidified. After being placed in the refrigerator overnight, some white crystals also precipitated from the solution and were separated mechanically from the tan solid. The crystals weighed 0.55 g which was 23 percent of the theoretical amount. Recrystallization from water gave the pure product, mp 154–155 C.

Analysis: Calculated for $C_{10}H_{10}N_3O_2Cl$: N, 17.53. Found: N, 17.42.

β-2'-(4'-Chlorobenzotriazolyl)-propionitrile

To a mixture of 1.00 g (0.0065 mole) of 4-chlorobenzotriazole and 4.00 g (0.0755 mole) of acrylonitrile was added 10 drops of pyridine. The resulting mixture was heated at 80 C for 20 hours, producing a brown, viscous material on cooling. The oil was dissolved in acetone and brought almost out of solution with hot water. The resultant solution was decolorized with norite and filtered, and the product allowed to recrystallize while cooling overnight in a refrigerator. Filtration produced 0.85 g of white solid that represented a 63 percent yield. Two subsequent recrystallizations from methanol gave the pure sample, mp 131.5–133.5 C.

Analysis: Calculated for $C_9H_7N_4Cl$: N, 27.11. Found: N, 26.94.

β-1'-(4'-Chlorobenzotriazolyl)-propionamide

To a melt of 1.15 g (0.0075 mole) of 4-chlorobenzotriazole and 0.55 g (0.0075 mole) of acrylamide was added 8 drops of benzyltrimethylammonium hydroxide (Triton-B). The solution was heated at 80 C for 20 hours, cooled, and ether was added to precipitate, after stirring, a white solid. The dried solid weighed 1.55 g representing 95 percent of the theoretical amount. Three recrystallizations from acetone gave the pure product, mp 166–168.5 C.

Analysis: Calculated for $C_9H_9N_4OCl$: Cl, 15.78. Found: Cl, 15.57.

β-Phenyl-β-1'-(4'-Chlorobenzotriazolyl)-propriophenone

4-Chlorobenzotriazole (1.53 g, 0.01 mole) and benzalacetophenone (2.08 g, 0.01 mole) were mixed and 4 ml of pyridine added. The mixture was heated at 90 C for 18 hours, cooled, 30 ml of ligroin and 10–20 ml of diethyl ether added, and the resulting mixture stirred until the oil solidified yielding a white solid. The filtered solid weighed 2.80 g for a 77.4 percent yield. One recrystallization from a diethyl ether–ligroin mixture and 1 from an acetone–water mixture gave the analytical sample, mp 139.5–141.5 C.

Analysis: Calculated for $C_{21}H_{16}N_3OCl$: C, 69.71; H, 4.46. Found: C, 69.65; H, 4.37.

β-2'-(4',6'-Dichlorobenzotriazolyl)-propionitrile

A mixture of 2.00 g (0.0106 mole) of 4,6-dichlorobenzotriazole, 6.00 g (0.113 mole) of acrylonitrile, and 5–7 drops of pyridine was heated at 80 C for 18 hours in a test tube fitted with a condensor and immersed in an oil bath heated with a glascol mantle. The reaction mixture was allowed to cool to room temperature and a white solid crystallized. The crystals were filtered, washed with a small amount of cold acrylonitrile, and dried to give 1.16 g of product, representing a 39 percent yield. The product was recrystallized twice from acrylonitrile to yield pure transparent crystals, mp 157–158 C.

Analysis: Calculated for $C_9H_6N_4Cl_2$: Cl, 29.41. Found: Cl, 29.71.

β-2'-(4',6'-Dichlorobenzotriazolyl)-propionamide

To a melt of 1.88 g (0.01 mole) of 4,6-dichlorobenzotriazole and 0.71 g (0.01 mole) of acrylamide was added 5–8 drops of Triton-B. The resulting mixture was heated at 80 C for 20 hours. The reaction mixture was cooled and 10–15 ml of diethyl ether added. After considerable stirring, a white solid formed that was filtered to yield 2.15 g of crude product, representing 83 percent of the theoretical amount. After 1 recrystallization from ethyl acetate and 2 from acetone, 0.20 g of white needles was isolated as an analytical sample, mp 214.5–217 C.

Analysis: Calculated for $C_9H_8N_4OCl_2$: C, 41.72; H, 3.11. Found: C, 41.78; H, 3.06.

β-2'-(4',6'-Dichlorobenzotriazolyl)-butyric acid

To a mixture of 1.88 g (0.01 mole) of 4,6-dichlorobenzotriazole and 1.00 g (0.01

mole) of crotonic acid (10% water) was added enough pyridine to produce a homogeneous solution that was heated at 100 C for 15 hours. Evaporation of the pyridine left an extremely viscous material that was poured into 0.5N hydrochloric acid and stirred to precipitate 1.75 g of crude product for a 64 percent yield. Two recrystallizations from acetone–water gave the analytical sample, mp 134–136 C.

Analysis: Calculated for $C_{10}H_9N_3O_2Cl_2$: N, 15.33; Neutr. equiv., 274.1. Found: N, 15.32; Neutr. equiv., 279.0.

β-Phenyl-β-2′-(4′,6′-Dichlorobenzotriazolyl)-propiophenone

To a melt of 1.88 g (0.01 mole) of 4,6-dichlorobenzotriazole and 2.08 g (0.01 mole) of benzalacetophenone (chalcone) was added 8 drops of Triton-B. The mixture was heated at 80 C for 20 hours. The reaction mixture was cooled, diethyl ether was added and, after stirring, 1.70 g of crude white product precipitated which represented a 43 percent yield. Two recrystallizations from diethyl ether gave 0.55 g of pure product, mp 160–162.5 C.

Analysis: Calculated for $C_{21}H_{15}N_3OCl_2$: C, 63.65; H, 3.82. Found: 63.89; H, 3.86.

4,5,6,7-Tetramethylbenzotriazole

Five g (0.0223 mole) of dinitroprehnitine was dissolved in 150 ml of glacial acetic acid, 0.5 g of palladium on charcoal was added and the solution was placed on the Parr hydrogenator overnight, producing tetramethyl-o-phenylenediamine. The reaction mixture was filtered and 25 ml of water was added. The resulting solution was cooled to 5–10 C and a sodium nitrite solution was added until an excess was observed. During addition of the sodium nitrite solution, a light tan precipitate could be seen forming. The precipitate was filtered, washed with water, dried, and found to weigh 2.50 g representing a yield of 73 percent. The sample was recrystallized from ethanol to give the pure product, mp 291–294 C.

Analysis: Calculated for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98; Neutr. equiv., 175. Found: C, 68.72; H, 7.39; N, 24.22; Neutr. equiv., 178.

β-2′-(4′,5′,6′,7′-Tetramethylbenzotriazolyl)-butyric acid

To a melt of 1.75 g (0.01 mole) of 4,5,6,7-tetramethylbenzotriazole and 1.00 g (0.01 mole) of crotonic acid (10% water) was added 20 drops of Triton-B. The mixture was heated at 100 C for 20 hours, cooled, and the viscous product was dissolved in 10–15 ml of acetone and poured into 0.5N hydrochloric acid to precipitate 2.00 g of crude product, representing a yield of 76.6 percent of the theoretical amount. The product was dissolved in 1 molar NaOH and filtered into acid in hopes of removing any unreacted 4,5,6,7-tetramethylbenzotriazole as residue on the filter. After several recrystallizations from an acetic acid–water mixture, the pure product was obtained, mp 207–208.5 C.

Analysis: Calculated for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33. Found: C, 64.10; H, 7.27.

Analytical Data

Elemental analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tennessee. The neutralization equivalent for 4,5,6,7-tetramethylbenzotriazole was obtained by using glacial acetic acid as the solvent, and as titrant, perchloric acid dissolved in glacial acetic acid. All other neutralization equivalents were determined using either water or ethanol–water mixtures to dissolve the sample and standard sodium hydroxide as the titrant. A Beckman Expandomatic pH meter was used in obtaining titration curves for detection of the end points.

Ultraviolet Absorption Spectra

Ultraviolet absorption data on all of the compounds were collected manually from a Beckman DU-2 spectrophotometer, using 10^{-4}–10^{-5} molar solutions of the sample dissolved in spectral grade methanol. The spectra for each of the parent benzotriazoles and their corresponding conjugate addition products are shown in Figs. 1, 2, and 3.

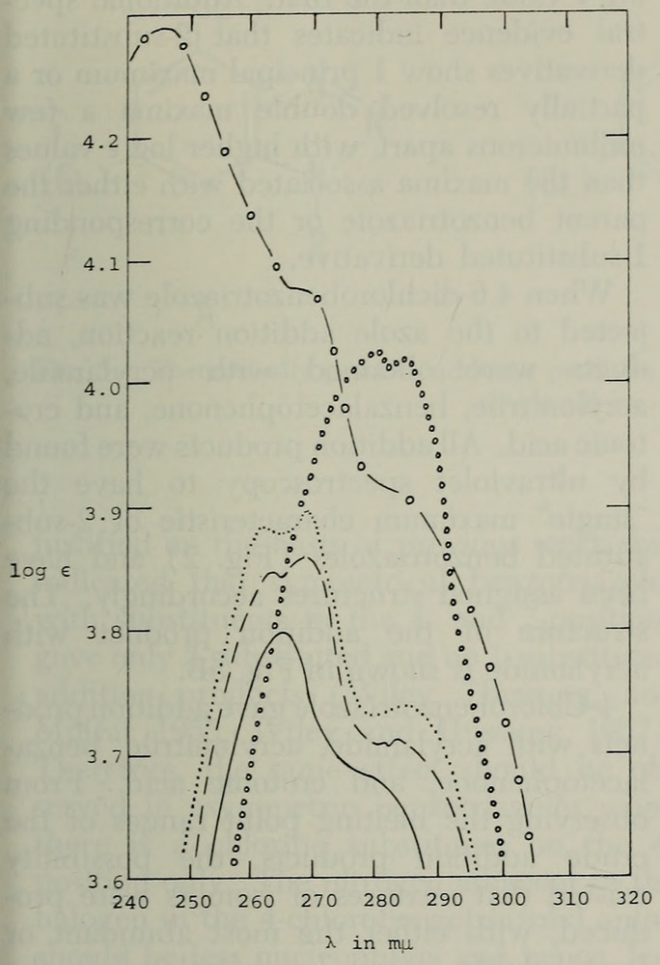

FIG. 1. Ultraviolet absorption spectra for 4-chlorobenzotriazole (———), β-1′-(4′-chlorobenzotriazolyl)-butyric acid (– – – –), β-2′-(4′-chlorobenzotriazolyl)-propionitrile (○ ○ ○), β-1′-(4′-chlorobenzotriazolyl)-propionamide (· · · · · ·), and β-phenyl-β-1′-(4′-chlorobenzotriazolyl)-propiophenone (–○–○–○–).

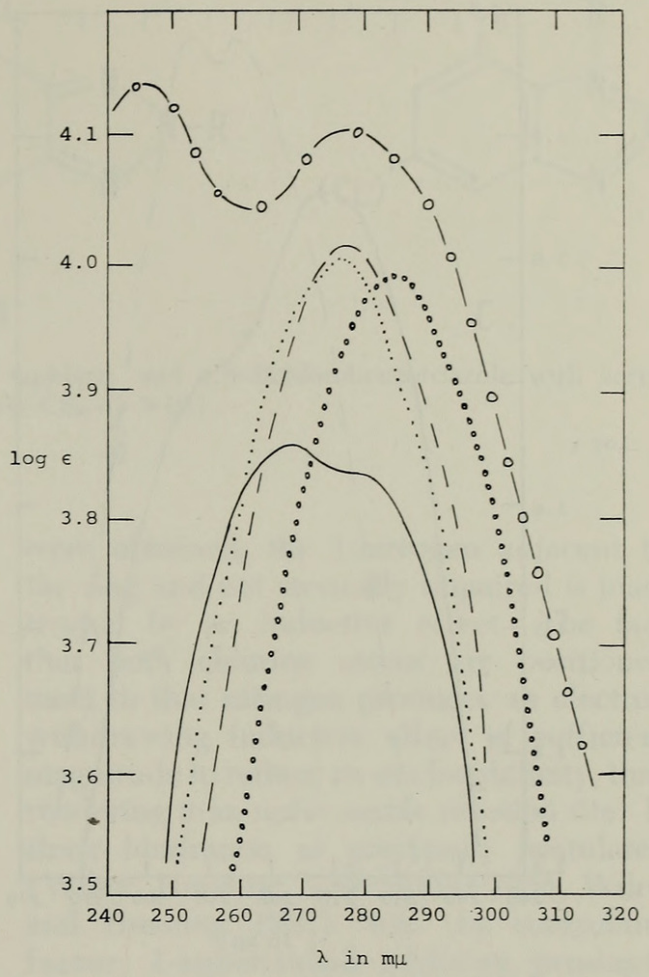

FIG. 2. Ultraviolet spectra for 4,6-dichlorobenzotriazole (———), β-2′-(4′-6′-dichlorobenzotriazolyl)-butyric acid (– – – –), β-2′-(4′,6′-dichlorobenzotriazolyl)-propionitrile (○ ○ ○), β-2′-(4′,6′-dichlorobenzotriazolyl)-propionamide (· · · · · ·), and β-phenyl-β-2′-(4′,6′-dichlorobenzotriazolyl)-propiophenone (–○–○–○–).

DISCUSSION

The ambident, nucleophilic anions of parent benzotriazoles are resonance stabilized. Resonance extremes for the anions of symmetrically substituted 4,7-dichlorobenzotriazole and asymmetrically substituted 4-chlorobenzotriazole are illustrated in Fig. 4.

In the 4,7-dichlorobenzotriazolyl anion, resonance extremes A and C (Fig. 4) are equivalent while in the 4-chlorobenzotriazolyl anion, resonance extremes A, B, and C (Fig. 4) are nonequivalent. As a result, the base-catalyzed azole addition reaction can theoretically give rise to 2 isomeric products with symmetrically substituted benzotriazoles and 3 isomeric products with asymmetrically substituted benzotriazoles (Fig. 5).

The problem of structural isomerism of the 1- and 2-substituted benzotriazoles has been resolved with benzotriazole. Ultraviolet absorption data distinguish between the 2 isomers and chemical data establish the position of the substituents (Krollpfeiffer et al. 1938, Specker and Gawrosch 1942). Further chemical and spectral evidence concerning 1- and 2-substituted benzotriazoles was provided from investigations involving 4,7- and 5,6-dichlorobenzotriazole, 4,5,6,7-tetrachloro- and 4,5,6,7-tetrabromobenzotriazole (Wiley, Hussung, and Moffat 1955; Wiley and Hussung 1957). The spectral

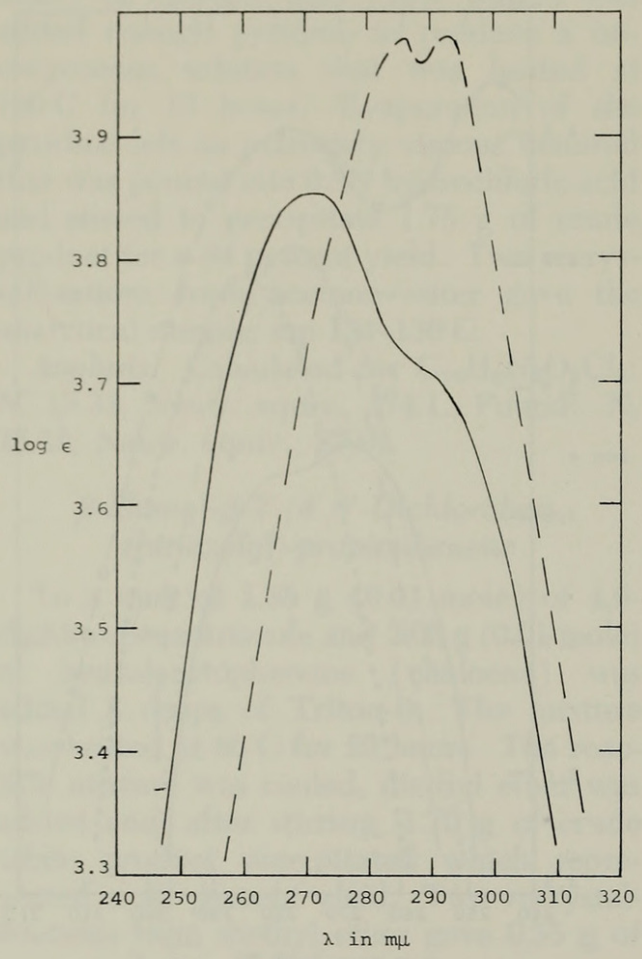

FIG. 3. Ultraviolet absorption spectra for 4,5,6,7-tetramethylbenzotriazole (———) and β-2′-(4′,5′, 6′,7′-tetramethylbenzotriazolyl)-butyric acid (– – –).

evidence indicates that benzotriazoles and their corresponding 1-substituted derivatives show two maxima approximately 20–25 mμ apart. In some spectra, a shoulder before the first maximum is observed. In all spectra, the second maximum is lower in log ε value than the first. Additional spectral evidence indicates that 2-substituted derivatives show 1 principal maximum or a partially resolved double maxima a few millimicrons apart, with higher log ε values than the maxima associated with either the parent benzotriazole or the corresponding 1-substituted derivative.

When 4,6-dichlorobenzotriazole was subjected to the azole addition reaction, adducts were obtained with acrylamide, acrylonitrile, benzalacetophenone, and crotonic acid. All addition products were found by ultraviolet spectroscopy to have the "single" maximum characteristic of 2-substituted benzotriazoles (Fig. 2) and have been assigned structures accordingly. The structure of the addition product with acrylamide is shown in Fig. 5B.

4-Chlorobenzotriazole gave addition products with acrylamide, acrylonitrile, benzalacetophenone, and crotonic acid. From observing the melting point ranges of the crude addition products, the possibility existed that mixtures of isomers were produced, with either the most abundant or least soluble isomer being isolated in the purification procedure. Limited attempts to separate isomers, however, were unsuccessful. Three of the adducts gave ultraviolet spectra characteristic of 1-substituted benzotriazoles while the acrylonitrile adduct gave a spectrum characteristic of 2-substitution (Fig. 1). The 1-substituted products could be either 1,4-disubstituted (Fig. 5A) or 1,7-disubstituted (Fig. 5C) but have been assigned the 1,4 structure. This seems

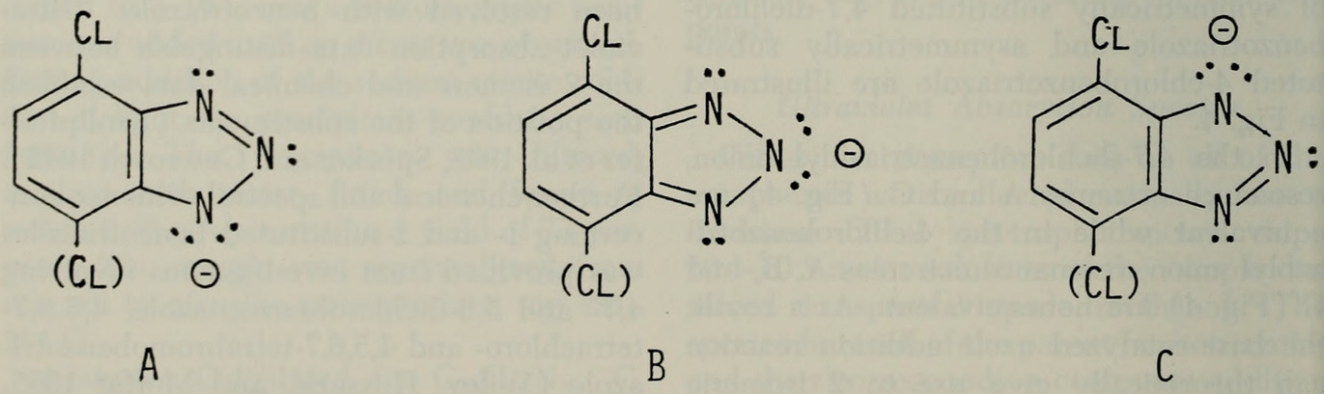

FIG. 4. Resonance extremes for 4-chloro- and 4,7-dichlorobenzotriazolyl anions.

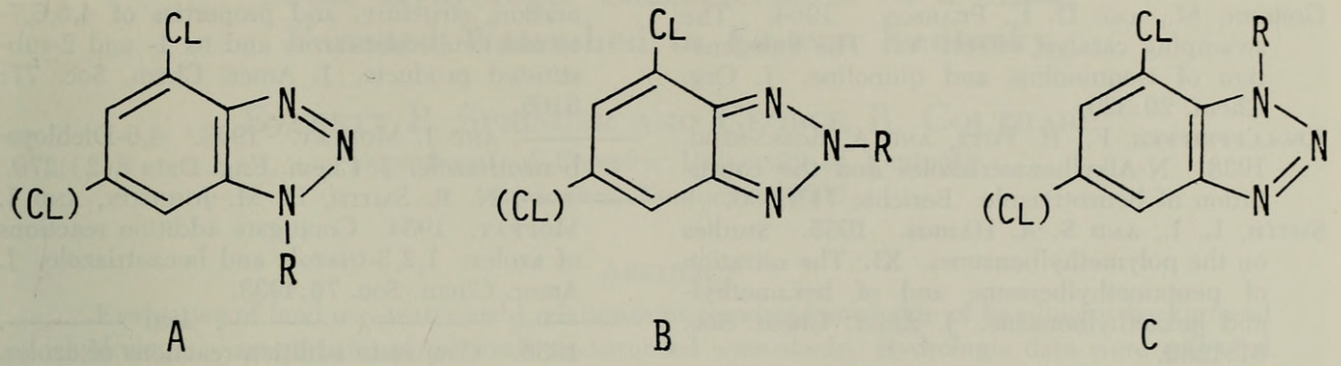

FIG. 5. Theoretically possible addition products of 4-chloro- and 4,6-dichlorobenzotriazole with acrylamide ($R = -CH_2-CH_2-\overset{\overset{O}{\|}}{C}-NH_2$).

justified on the basis of previous work that indicated that symmetrical benzotriazoles with substituents in the 4- and 7-positions gave only 2-substituted and no 1-substituted addition products (Wiley, Hussung, and Moffat 1955; Wiley and Hussung 1957). Therefore, the same effect should be observed in asymmetric benzotriazoles when there is a chlorine substituent on the 4-position only. The nitrogen adjacent to the halogen in the 4-chlorobenzotriazolyl anion should be less nucleophilic, and hence, less favorable as a reaction site in the addition reaction, since the chlorine would reduce the electron density at that nitrogen, inductively, and could, as previously postulated, sterically impair attack at that position.

The slightly acidic nature of benzotriazoles is attributable to resonance stabilization of their anions. Decreased acidity in 4,5,6,7-tetramethylbenzotriazole, due apparently to the electron releasing character of the methyl groups, made attempts at titration with dilute base unsuccessful. This reduced acidity made the preparation of base-catalyzed conjugate addition products difficult. 4,5,6,7-Tetramethylbenzotriazole was added successfully, however, to crotonic acid. The addition product formed was indicated by ultraviolet absorption data to be 2-substituted (Fig. 3).

The best insight into the effect of benzenoid substituents of benzotriazoles on the course of the addition reaction was provided by the studies involving 4,6-dichlorobenzotriazole. Since only 2-substituted products were obtained, the 1-nitrogen adjacent to the ring and not sterically impaired is inactivated by an inductive effect. The fact that both chlorine atoms are positioned meta to that nitrogen produces an electron withdrawing inductive effect of sufficient magnitude to reduce its nucleophilicity, thus rendering it an unfavorable reaction site. If steric hindrance, as previously postulated (Wiley, Hussung, and Moffat 1955; Wiley and Hussung 1957), was the controlling factor, 1-substituted addition products would no doubt have been produced. The fact that 4-chlorobenzotriazole gave both 1- and 2-substituted addition products can be explained on the basis of a smaller inductive effect and the absence of steric interference at the 1-nitrogen.

The presence of electron releasing methyl groups in the 4- and 7-positions should favor inductively, and hinder sterically, the involvement of the 1-(3-) nitrogens in the addition reaction. Since 4,5,6,7-tetramethylbenzotriazole gave a 2-substituted addition product, it appears, on the basis of this evidence, that the steric factor plays the dominant role.

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